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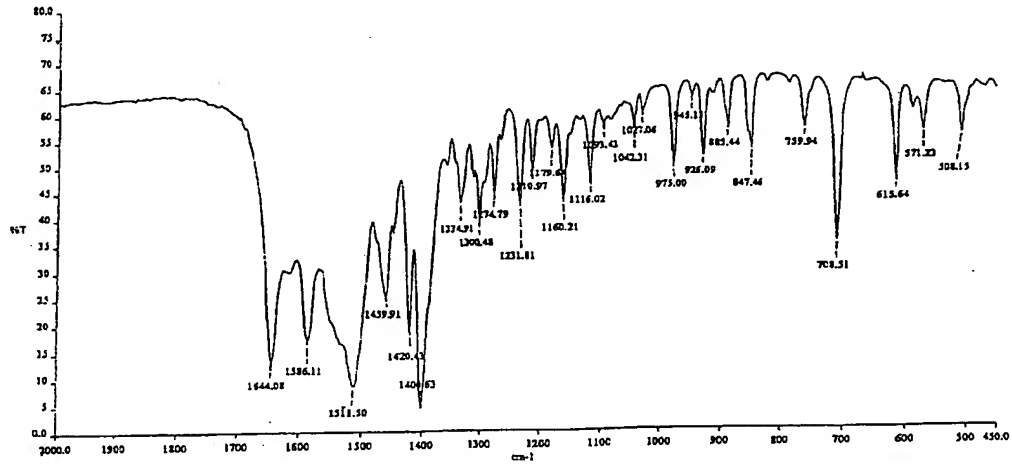
(54) Title: A PROCESS FOR THE PREPARATION OF GABAPENTIN FORM-II



(57) Abstract: The present invention relates to a new industrial feasible process for the preparation of Gabapentin Form-III by reacting 1,1-cyclohexane diacetic acid mono amide with alkali hypohalite followed by acidification with acids in presence of an organic solvent, extracting the liberated acid salt into that solvent followed by addition of an ante solvent to crystallize the Gabapentin acid salts. The separated salt is then suspending in organic solvent(s) and pH is adjusted with a base(s) at a specified temperature range, cooled to ambient temperature, followed by separation of Gabapentin Form-III, which is further converted to Gabapentin Form-II by slurrying in ethanol at specified temperature.

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GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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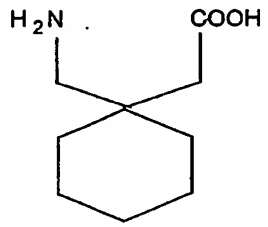
A process for the preparation of Gabapentin Form-II

The present invention relates to a process for preparing Gabapentin Form-III and its use for the preparation of Gabapentin Form-II.

Gabapentin (i.e. 1-aminomethyl-1-cyclohexaneacetic acid), is the active principle



Gabapentin

mainly used for the treatment of convulsive type cerebral disorders, such as epilepsy, hypokinesia including fainting and other brain trauma and in general, it is deemed to produce an improvement in the cerebral functions. Commercially available Gabapentin is crystalline and exhibits various polymorphic Forms such as monohydrate; Form-II and Form-III characterized by their typical IR and X-ray diffraction patterns.

Several processes for the preparation of Gabapentin are reported in literature; US Patent Nos. US 4,087,544 and US 4,024,175 discloses some preparation methods starting from cyclohexane-1, 1-diacetic acid. They also discloses an acid salt Gabapentin hydrochloride hydrate in a stoichometric ratio of 4:4:1 and a sodium salt of Gabapentin hydrate in a stoichometric ratio of 2:1. US Patent No. US 4,894,476 and US Patent No. US 4,960,931 discloses a method for converting the hydrochloride salt into a crystalline monohydrate by eluting the aqueous solution through a basic ion-exchange resin, producing a slurry from the elute, adding an alcohol to the slurry and isolating the final product by centrifuging followed by drying.

Our co-pending Indian Patent Application No 330/MAS/2003 discloses a method for the conversion of Gabapentin acid addition salts into Gabapentin Form-II directly by neutralization with base in a solvent at specified temperatures.

PCT Publication WO 98 / 28,255 discloses a method for the preparation of Gabapentin Form-III from Gabapentin hydrochloride. The process involves the dissolution of Gabapentin hydrochloride salt in an organic solvent (Iso-propyl alcohol) by mixing at 25°C for 30 min. followed by the addition of carbon, subjected to mixing for 2 hrs, followed by removal of inorganics by filtration. The solvent is then removed from the filtrate to obtain the solid so obtained is dried in vacuum at temperature not to exceed 35°C. The dried residue is then treated with a second solvent and a base, mixed for 2hrs at 25°C followed by filtration and drying yielding Gabapentin Form-III.

Form-III is converted to Form-II either by suspending Form-III in methanol at 25°C for about 14 hrs followed by filtration and drying under vacuum at 35°C or by suspending the humid cake of Form-III in methanol, refluxing followed by cooling to 34°C, Crystallization is induced by seeding with pure Form-II for 60 min. followed by cooled to 25°C, evaporating off the methanol in vacuum at temperature below 25°C, cooling to 0°C – 10°C and maintaining the system at the temperature for 2hrs, followed by filtration and vacuum drying at 35°C.

The method of conversion of Gabapentin hydrochloride to Form-III as disclosed in PCT Publication WO 98 /28,255 involves extensive work-up procedures such as complete distillation of the first solvent up to dryness under vacuum at low temperature, followed by the treatment using a second solvent and a base and finally isolating Form-III. Such multi step processes increase the number of solvents to be handled thereby enhancing cost of production. Further conversion of Form-III to Form-II by the published process involves long processing time and extensive operations such as seeding with pure Form-II to induce crystallization followed by removal of methanol under vacuum at 25°C, isolation of the

product by cooling, maintaining the system at specified temperatures for long periods, filtration and drying.

There is a long-standing need in industry to develop operationally cost effective processes for the preparation of Gabapentin Form-III and its conversion to Gabapentin Form-II.

There is a long-standing need in industry to develop operationally cost effective processes for the preparation of Gabapentin Form-III and its conversion to Gabapentin Form-II.

Another object of the invention is to provide an elegant process for the preparation of Gabapentin Form-II from the Gabapentin hydrochloride via Gabapentin Form-III.

Yet another object of the invention is to provide an elegant process for the preparation of Gabapentin Form-II from the Gabapentin hemisulphate hemihydrate via Gabapentin Form-III.

Thus in accordance of this invention, 1,1-Cyclohexane diacetic acid monoamide is reacted with alkali hypo halite followed by acidification with acids in presence of an organic solvent to extract the liberated acid salts into that solvent followed by the addition of an ante solvent to crystallize the Gabapentin acid salts. The separated salts is then suspending in organic solvent(s) and pH is adjusted with base(s) in a specified temperature range, cooled to ambient temperature, followed by separation of Gabapentin Form-III which is further converted into Gabapentin Form-II by slurrying in ethanol at specified temperature.

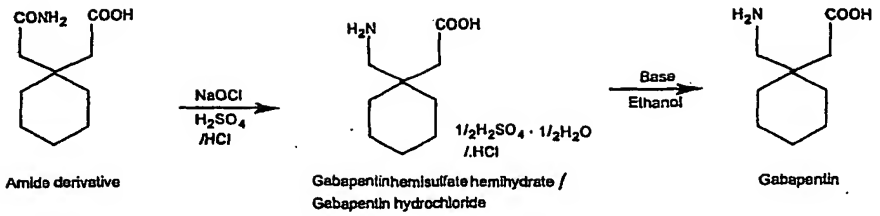


Fig.1 X-ray diffraction pattern of the Gabapentin Form -II

Fig.2 FTIR spectrum of the Gabapentin Form - II

Fig.3 X-ray diffraction pattern of the Gabapentin Form-III (prepared as per the example-1)

Fig.4 FTIR spectrum of the Gabapentin Form –III (prepared as per the example-1)

Fig.5 X-ray diffraction pattern of the Gabapentin Form-III

Fig.6 FTIR spectrum of the Gabapentin Form-III

Table-1.FTIR peaks of Gabapentin Form-I, Form-II and Form-III

S.No	Form-I (Hydrate)	Form-II	Form-III
1	1664		1664
2	1624	1615	1586
3		1546	1510
4	1542	1476	1460
5		1420	1420
6		1400	1402
7		1337	1333
8		1327	1,311
9	1292	1300	1290
10	1175	1165	1180
11	1154	1,133	1160
12	968	1120	1115
13		976	974
14	926	928	945
15	880	922	926
16	726	890	885
17	648	749	760

XRD peaks and 2 theta values:

S.No	Form-I (Hydrate)	Form - II	Form- III
1	6.1	7.8	6.1
2	12.2	13.3	12.1
3	16	14.9	16.9
4	18.3	16.6	17.6
5	19.1	16.8	18.1
6	19.8	19.5	19.9
7	20.7	20.2	20.8
8	24.5	21.3	24.4
9	26.4	21.8	25.1
10	28.4	23	28.8
11	30.7	23.5	30.2
12	32.3	25.7	30.7
13		26.9	31.5
14		28	

The process according to the present invention comprise steps:

- Dissolution of Gabapentin acid salts in a short chain alcohol
- Separation of the insolubles if any
- pH adjustment of the solution with base(s) at specified temperature
- Maintaining the reaction mass in a specified temperature range for a certain period
- Cooling the reaction mass to room temperature
- Separation of the formed Gabapentin Form-III
- Slurrying of Gabapentin Form-III in ethanol and raising the temperature and stirring for certain duration.
- Cooling the reaction mass to room temperature and stirring for certain duration
- Separation of Gabapentin Form-II followed by drying.

XRD and IR is used to characterize the products of the process.

1,1-cyclohexane diacetic acid mono amide used as starting material is prepared as per the literature (US Patent No. US 4,024,175).

Reaction of 1,1-cyclohexane diacetic acid mono amide with sodium hypo chlorite solution in the temperature range of -10^0C to 5^0C, followed by acidification of the reaction mass to pH below 2 with a mineral acid preferably with hydrochloric acid or sulphuric acid in presence of n-Butanol in a temperature range of 15^0C to 25^0C.

The reaction mass is allowed to settle and the organic layer is separated. The aqueous layer is extracted few times with the organic solvent. The combined extracts is dried over dehydrating agents and the dried organic layer is diluted with ante solvent(s) selected from hydrocarbons, aromatic hydrocarbons, alkyl ketones, alkyl ethers, etc. The preferred solvent is hexane, toluene, acetone, di isopropyl ether or their mixtures. The reaction mass is cooled to precipitate the acid addition salt(s). The precipitated Gabapentin acid addition salt(s) is separated and dried to constant weight.

Gabapentin acid addition salt(s) is dissolved in short chain alcohols, preferred alcohol being ethanol, n-propanol, iso propanol, and n-butanol at 20^0C to 50^0C. The solution is stirred to get a clear solution. Insolubles if any are filtered off and pH adjustment of the filtrate is done with base(s). The preferred bases are triethyl amine, di isopropyl ethylamine, etc. The precipitated Gabapentin Form-III is separated wash the solvent of the reaction medium, dried in a preferred temperature range of 45^0C – 50^0C.

The Gabapentin Form-III is further converted into Form-II by suspending Form- III in alcohol, raising the temperature to 60^0C – 75^0C, maintaining the system at this temperature for 1 to 6 hrs, followed by gradual cooling and stirring for 1 – 2 hrs at temperature 20^0C – 25^0C. The product is separated and dried to obtain Gabapentin Form-II of pharmaceutically acceptable quality.

The invention is now illustrated with a few non-limiting examples.

EXAMPLE – I:

Stage – 1: Preparation of Gabapentin Hydrochloride

Sodium hydroxide (51 g) is dissolved in sodium hypochlorite solution (6.25%, 625 G) and cooled to 10^0C. The solution is stirred for 10 – 15 min, and further cooled to -5^0C. In a separate flask, 1,1-cyclohexane diacetic acid monoamide (100 g) is dissolved in 4N Sodium hydroxide solution (150 ml) at 15^0C – 20^0C. The amide solution is slowly added to the sodium hypochlorite solution at temperature -5^0C to -3^0C. The solution is then maintained at about 0^0C for 2 hrs. The temperature is gradually raised over 3 hrs to 20^0C – 25^0C and then maintained at this temperature for 4 hrs. Sodium meta bisulphite solution (5 g in 10 ml water) is then added to the solution. The reaction mass is filtered remove any un-dissolved material. pH of the filtrate is adjusted to around 9.0 by the addition of hydrochloric acid at temperature 20^0C – 25^0C. n-Butanol (200 ml) is added and the pH is further adjusted to 1.5 with hydrochloric acid and stirred for 10 – 15 min. The reaction mass is allowed to settle with separation of the layers. The aq. Layer is extracted with n-Butanol (200 ml). The organic is dried over anhydrous sodium sulphate (15 g). Di isopropyl ether (1200 ml) is slowly added to the dried organic layer at room temperature over 30 – 45 min and maintained for about 1 hr under stirring. The system is cooled to 5^0C and stirred for 1 hr at 0^0C – 5^0C.

Product is filtered, washed with di iso propyl ether (50 ml) and dried at 45^0C – 50^0C to constant weight and finally crystallized from tertiary butanol – Diisopropyl ether to get the pure hydrochloride.

The dry wt of the hydrochloride salt is 80.0 g (Yield: 75.0%)

Stage–2: Preparation of Gabapentin Form-III from Gabapentin hydrochloride

The Gabapentin hydrochloride salt (100 g) prepared in stage-1 is suspended in n-propanol (1000 ml) and stirred for 20 min at room temp. Filtered the mass to remove insolubles if

any. The filtrate is slowly heated to 35^{0}C - 40^{0}C and pH is adjusted to 7.2 by slow addition of di isopropyl ethylamine solution (180 ml in 180 ml of n-propanol) at 35 - 40^{0}C over 40 min. The reaction mass is gradually cooled to 20^{0}C – 25^{0}C over 30 min. The product is filtered, washed with n-propanol (50 ml) and dried at 45^{0}C – 50^{0}C to constant weight.

Dry wt of the Gabapentin Form-III is 49.5 g corresponding to yield of 62%.

XRD and IR spectral data are given in table 1

Stage –3: Preparation of Gabapentin Form-II from Gabapentin Form-III.

Gabapentin Form-III (40 g) prepared in stage - 2, is suspended in ethanol (280 ml) and the temperature is raised to 70^{0}C and maintained for 90 min. at 70^{0}C – 75^{0}C. The reaction mass is gradually cooled to room temperature and stirred for 30min. The product is filtered, washed with ethanol (20 ml) and dried at 50^{0}C – 55^{0}C to constant weight.

Dry wt of the Gabapentin Form-II is 34.4 g , corresponding to 86.0% yield.

EXAMPLE - II

Stage – 1: Preparation of Gabapentin hemisulphate hemihydrate

Sodium hypochlorite solution (6.25%, 625 g) is cooled to 10^{0}C and sodium hydroxide flakes (51 g) is dissolved in it by stirring for 10 – 15 min. at 10^{0}C – 15^{0}C. The mass is further cooled to –5^{0}C. In a separate flask1, 1-cyclohexane diacetic acid monoamide (100g) is dissolved in 4N sodium hydroxide solution (150 ml) at 15^{0}C – 20^{0}C. The amide solution is slowly added to sodium hypochlorite solution at temperature –5^{0}C to –3^{0}C over 3hrs and then maintained at about 0^{0}C for 2 hrs. The temperature is slowly raised to 20^{0}C – 25^{0}C over 3 hrs and maintained for 4 hrs at 20^{0}C – 25^{0}C. Sodium metabisulphite solution (5 g in 10 ml water) is then added. The reaction mass is filtered to remove any undissolved material. pH of the filtrate is adjusted to 9.0 by the addition of 1:1 dilute sulphuric acid at

temperature 20°C – 25°C. n-Butanol (200 ml) is added and the pH id further adjusted to 1.5 with dilute sulphuric acid. The reaction mass is stirred for 10 – 15 min. and then allowed to settle. The layers are separated. The aqueous layer is extracted with n-Butanol (200 ml). The combined extract is dried over anhydrous sodium sulphate (15 g). Di isopropyl ether (1200 ml) is slowly added at room temperature over 30 – 45 min to the dried extracted layer. The reaction mass is stirred for 1 hr and then cooled to 5°C and stirred for 1 hr at about 0°C – 5°C. The product is filtered, washed with di isopropyl ether (50 ml) and dried at 45°C – 50°C to constant weight.

The yield of dry wt of hemisulphate hemihydrate is 85 g (Yield: 73.8%).

Stage–2: Preparation of Gabapentin Form-III from Gabapentin hemisulphate hemihydrate

The Gabapentin hemisulphate hemihydrate salt (100 g) in stage-1 is suspended in ethanol (700 ml) and stirred for 30 min. at room temperature. The insolubles is filtered and washed with ethanol (50 ml). The filtrate is heated to 40°C – 45°C and the pH of the filtrate is adjusted to 7.3 by slow addition of di isopropyl ethylamine solution (135 ml in 145 ml ethanol) at 40°C - 45°C over 20 min. The reaction mass is then immediately cooled to 20°C – 25°C over 30 min. The filtered product is washed with ethanol (50 ml) and dried at 45°C – 50°C to constant weight.

Dry wt of the Gabapentin Form-III is 49.5 g corresponding to Yield of 62 %.

XRD and IR spectral data are given in table 1

Stage –3: Preparation of Gabapentin Form-II from Gabapentin Form-III.

The Gabapentin Form-III (40 g) prepared is suspended in ethanol (240 ml) and the temperature is raised to 65°C and maintained for 60 min. between 65°C – 70°C. The mass

is cooled to room temperature and stirred for 30min. at room temperature. The filtered product is washed with ethanol (25 ml) and dried at $50^0C - 55^0C$ to constant weight.

The dry weight of the Gabapentin Form-II is 35 g corresponding to 87.5% yield.

Claims:

1. A process for the preparation of Gabapentin Form-II via Form-III comprising steps:
   - Dissolution of Gabapentin acid salts such as Gabapentin hydrochloride or Gabapentin hemisulfate hemihydrate in a short chain alcohol
   - Separation of the insolubles if any
   - pH adjustment of the solution with base(s) in a temperature range of 20^0C to 50^0C
   - Cooling the reaction mass to room temperature
   - Separation of the formed Gabapentin Form-III
   - Slurrying of Gabapentin Form-III in ethanol, in a temperature range of 60^0C to 75^0C and maintaining for 1 to 6 hrs
   - Cooling the reaction mass to room temperature and stirring for 30 to 120 minutes
   - Separation of Gabapentin Form-II followed by drying

2. A process as claimed in claims 1, wherein the short chain alcohol is selected from ethanol, n-propanol, iso- propanol and butanol

3. A process as claimed in claims 1, wherein the base(s) is selected from disiopropyl ethylamine, triethylamine and tributylamine.

4. A process as claimed in claims 1, wherein pH is adjusted to 6.8 - 8.2 in a temperature range of 35^0C to 45^0C.

5. A process as claimed in claim 1, the alcohol used for the slurrying Gabapentin Form-III is selected from ethanol, n-propanol and Iso propanol.

6. A process as claimed in claim 1, wherein the temperature is in the range of 70^0C to 75^0C for conversion of Form- III to Form-II.

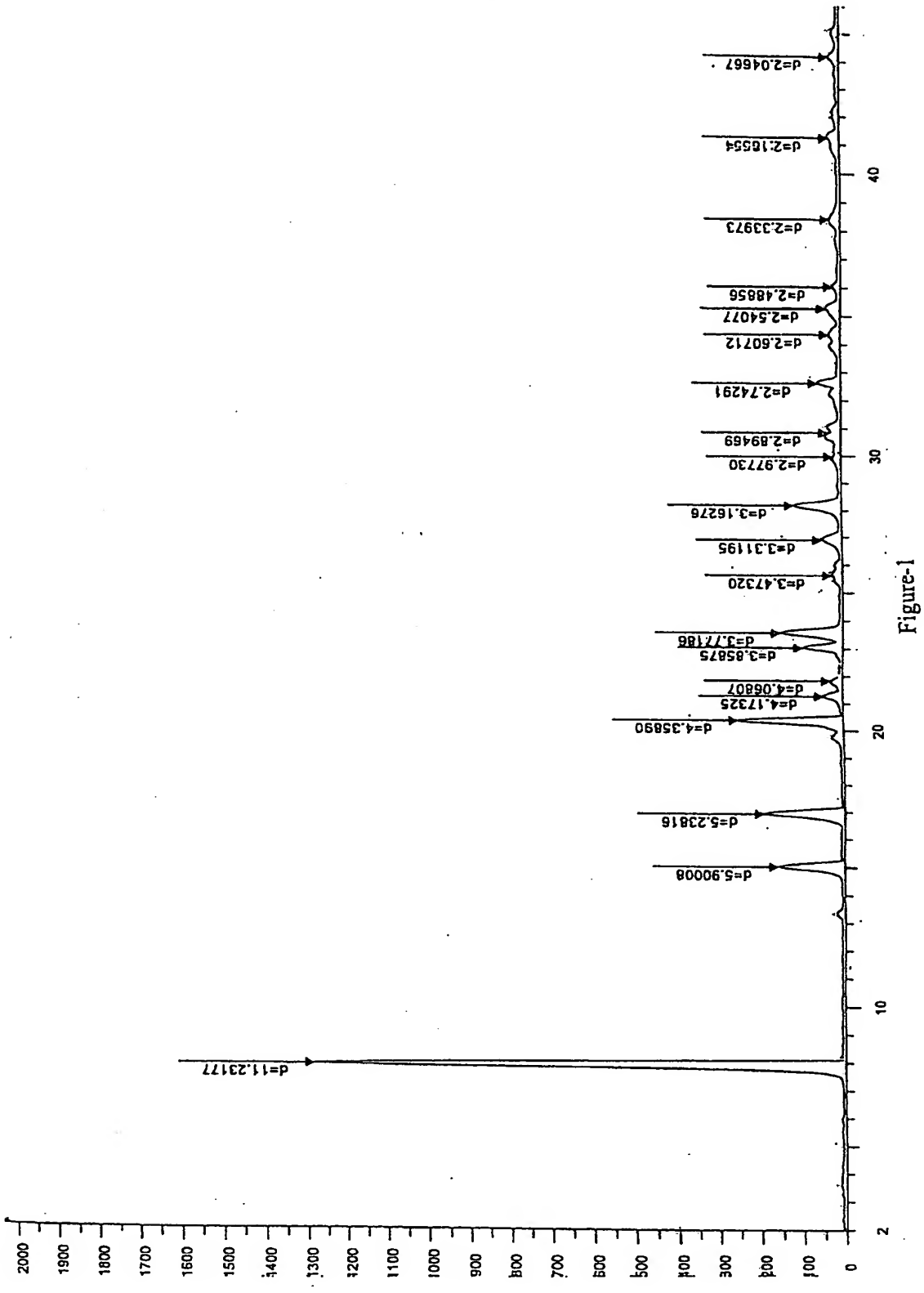

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Figure-1

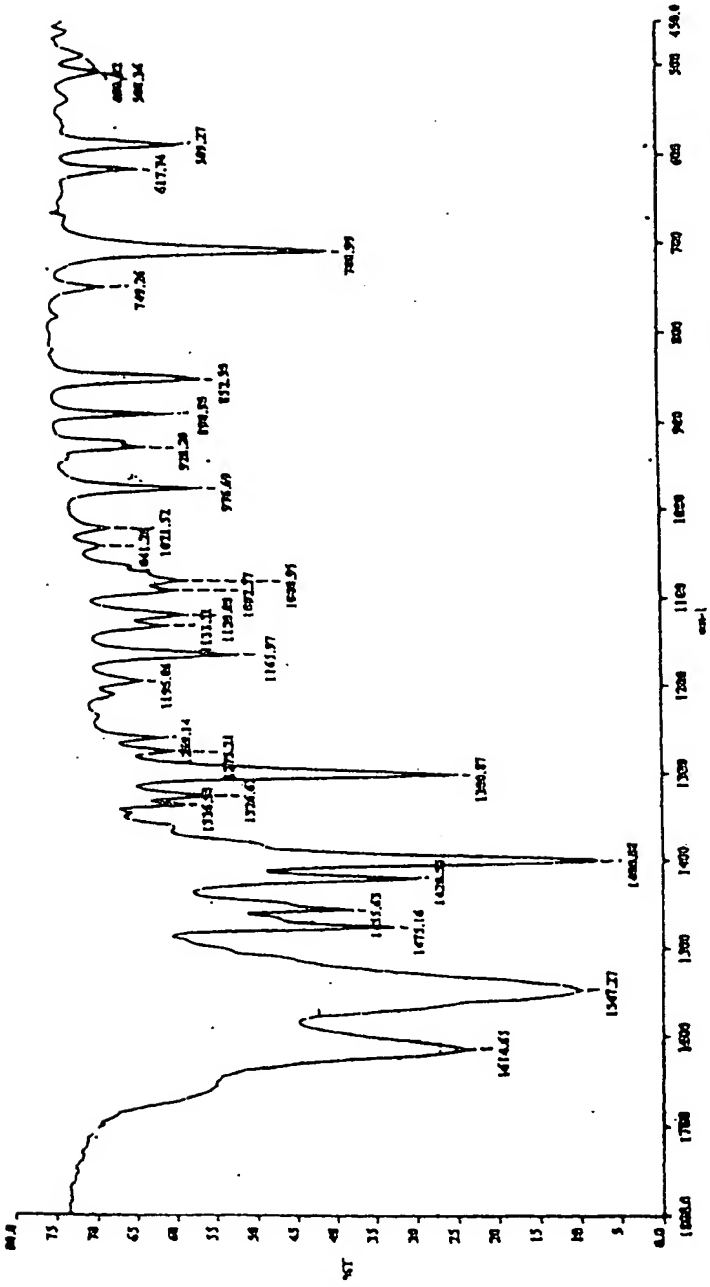


Figure-2

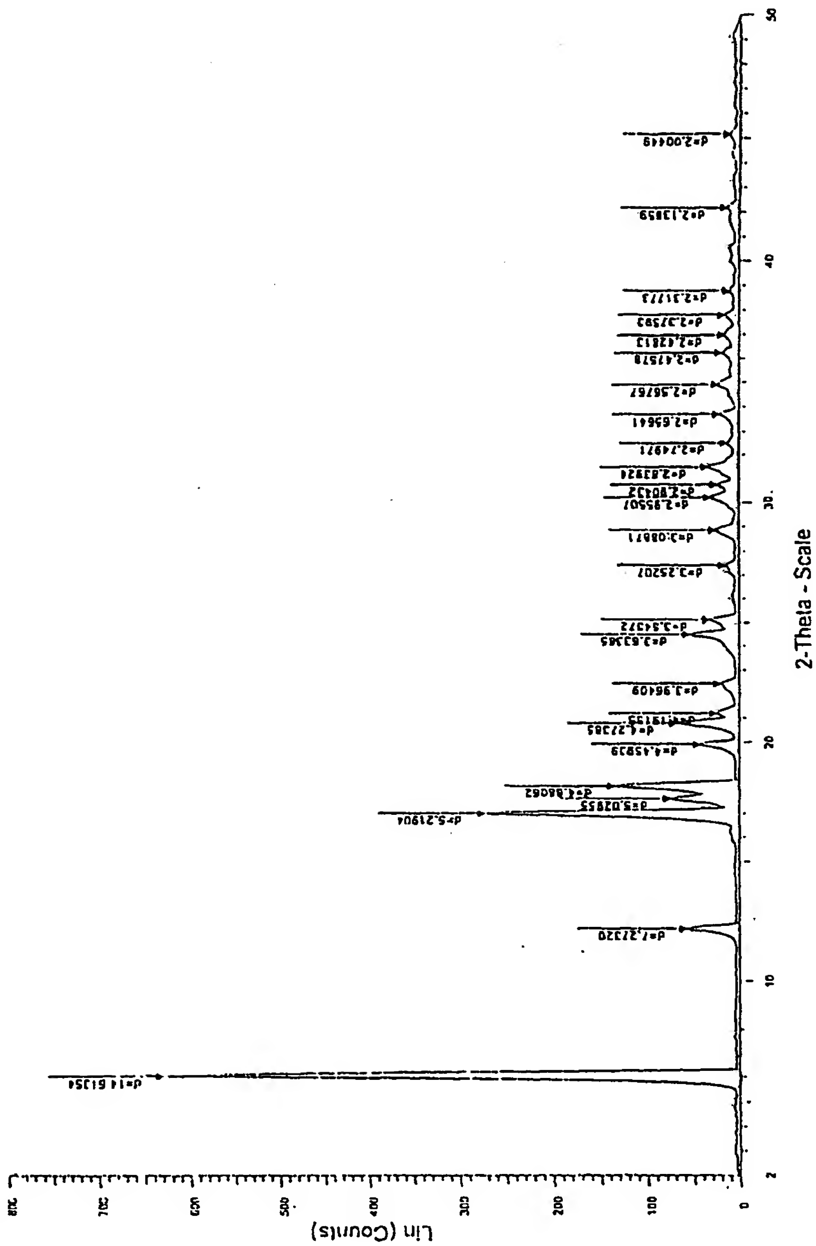
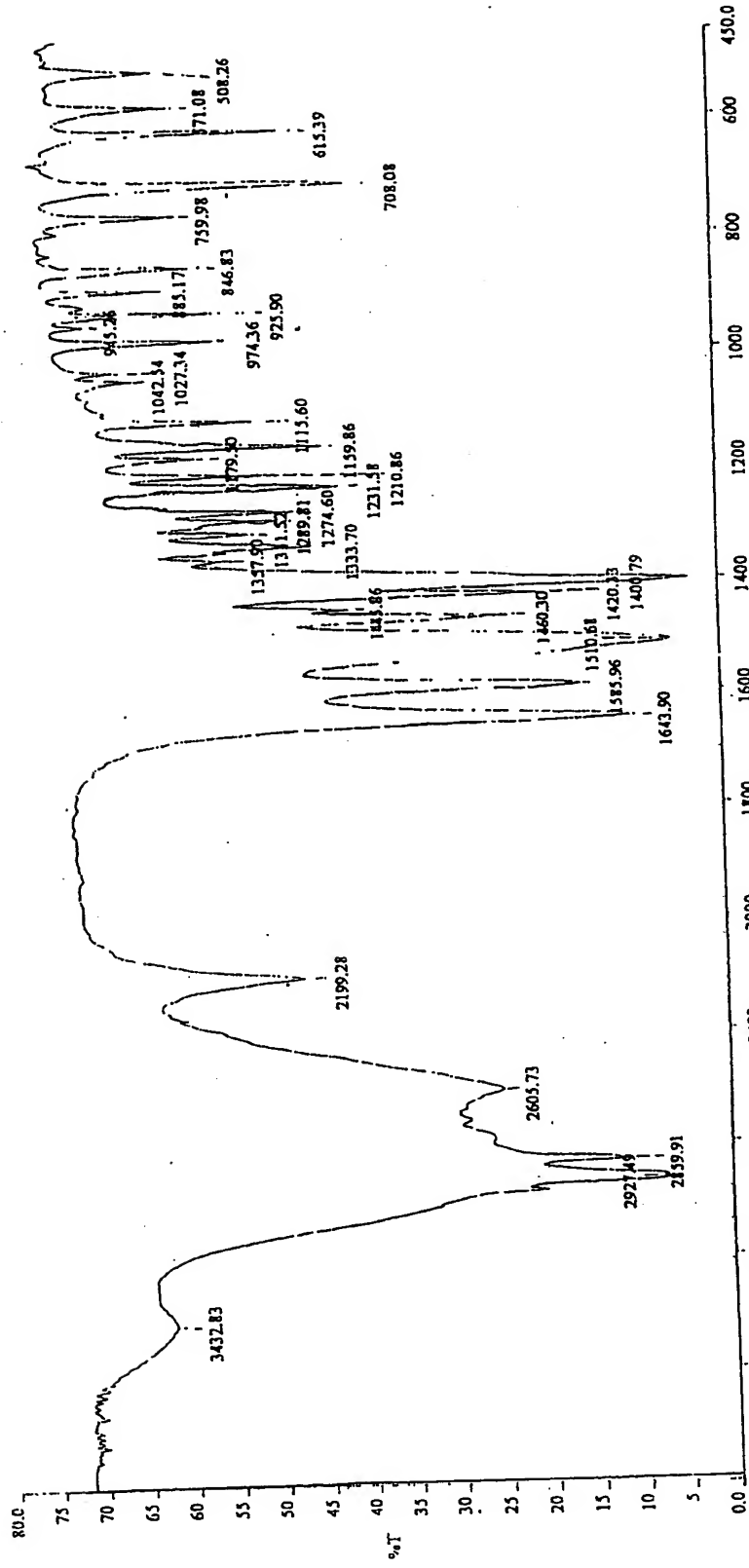


Figure-3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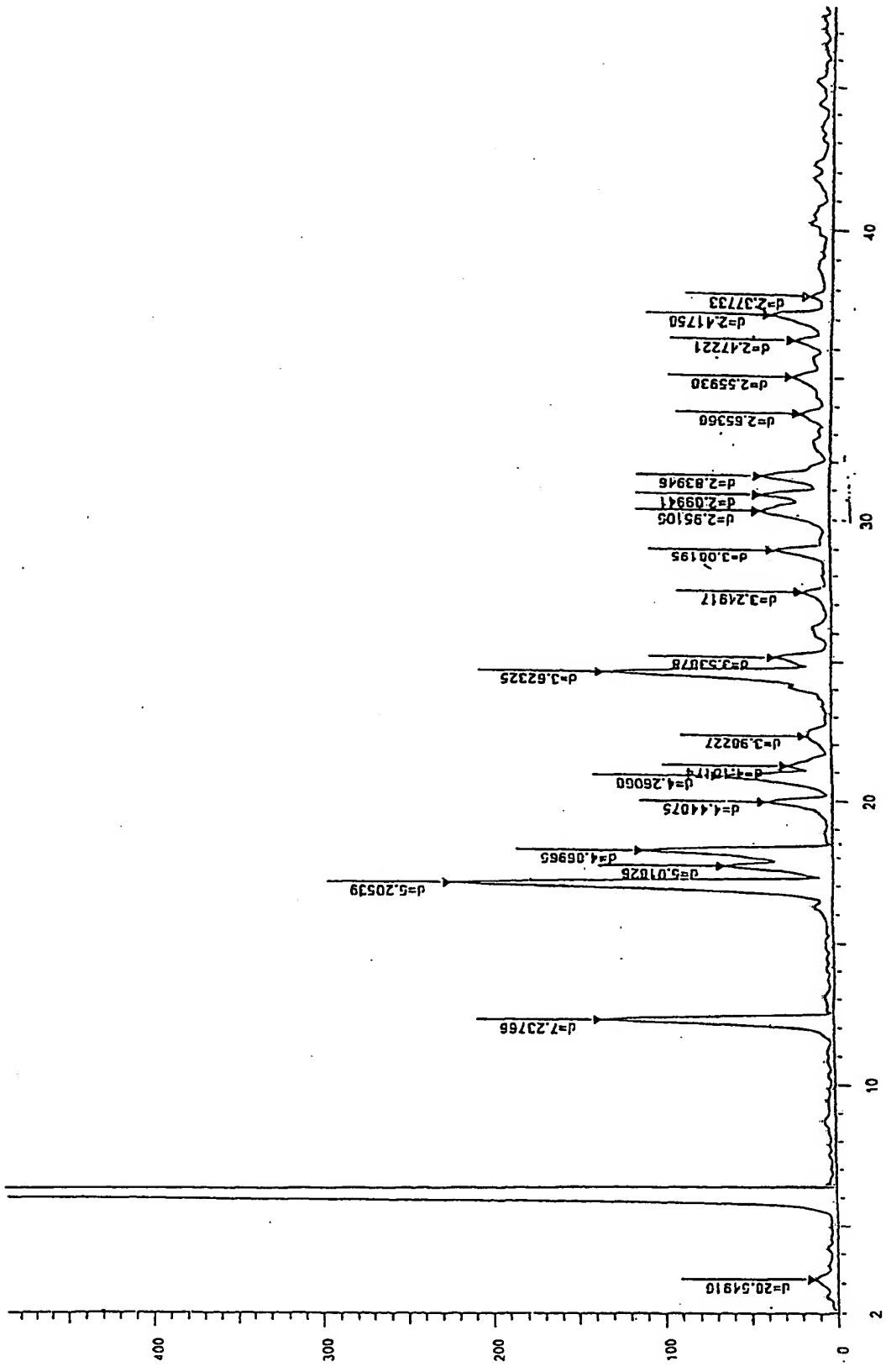
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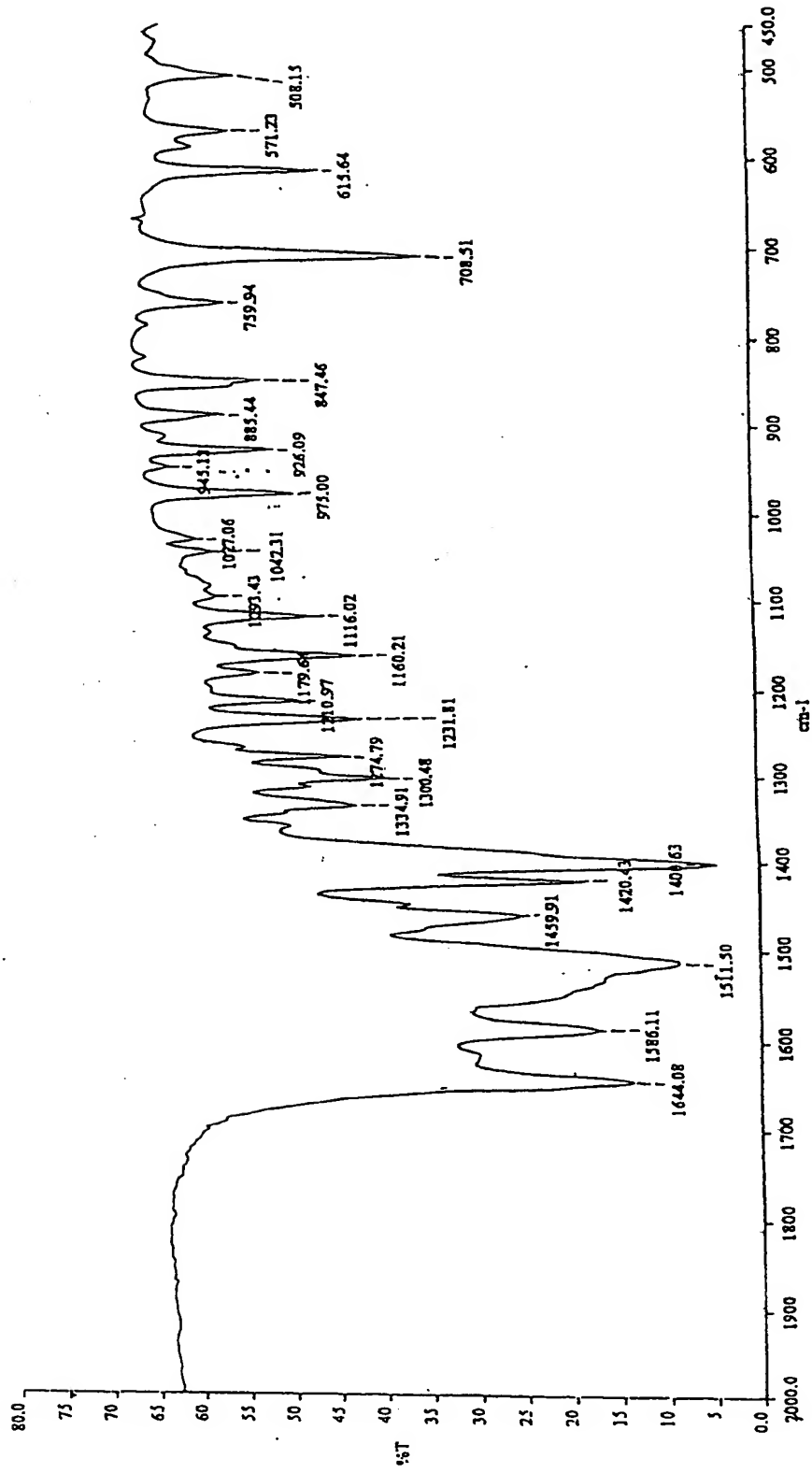
Figure-5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1042.31
975.00
926.09
885.44
847.46
759.84
708.51
613.64
571.23
508.15

Figure-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2004/000103

A. CLASSIFICATION OF SUBJECT MATTER
IPC[7]: C07C 229/28, 227/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC[7]: C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY, CAPLUS, WPI, EPODOC, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO1998/028255 A (TEVA PHARMA) 2 July 1998 (02.07.1998); *claims 1-7; examples 1A, 1B, 1C, 13, 16 (cited in the application).*	1-6

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 2004 (14.10.2004)	25 October 2004 (25.10.2004)
Name and mailing address of the ISA/ AT **Austrian Patent Office** Dresdner Straße 87, A-1200 Vienna Facsimile No. +43 / 1 / 534 24 / 535	Authorized officer MÜLLER-HIEL R. Telephone No. +43 / 1 / 534 24 / 434

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 2004/000103

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO A 19980282 55		none	